Infliximab as a Treatment for Rheumatoid arthritis - Prevention of Structural Damage

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FDA Review Team

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Overview of Presentation

- Indication, Dose
- Background of Pivotal Clinical Trial - ATTRACT
- Review of Radiographic Data
- Review of Clinical Data

Current Indication - Rheumatoid arthritis

Remicade in combination with methotrexate, is indicated for the reduction in signs and symptoms of rheumatoid arthritis in patients who have had an inadequate response to methotrexate

Proposed Indication

Remicade, in combination with methotrexate, is indicated for the reduction in signs and symptoms, the prevention of structural damage (erosions and joint space narrowing) and improvement in physical function in patients with rheumatoid arthritis who have had an inadequate response to methotrexate.

Dose regimen - Rheumatoid arthritis

- 3 mg/kg given as an intravenous infusion
- additional 3 mg/kg doses at 2 and 6 weeks after the first infusion
- then every 8 weeks thereafter
- Remicade should be given in combination with methotrexate

Background - ATTRACT

- 2 year study
- Infliximab as adjunct therapy to MTX in patients with active disease despite 3 months treatment with MTX

Treatment Groups in ATTRACT

- Five treatment groups:
  - » Placebo (MTX alone)
  - » Infliximab - 3 mg/kg q 4 weeks
    - 3 mg/kg q 8 weeks
    - 10 mg/kg q 4 weeks
    - 10 mg/kg q 8 weeks
- Study drug infusions:
  - » Weeks 0, 2, and 6 then q 4 weeks
- All in conjunction with ≥ 12.5 mg/week MTX

Endpoints in ATTRACT

- Week 30 - improvement in signs and symptoms
- Weeks 54 and 102- prevention of structural damage
- Week 102 - improved physical disability

Patient Population in ATTRACT

- 428 patients
- 34 sites: 22 North American, 12 European
- Baseline demographics:
  - » 78% women
  - » 91% White, 5% Black, 1% Asian
  - » median age = 54 (range: 19-80)

Baseline Disease Characteristics

- Balanced ACR criteria across treatment groups
- Median duration = 8.4 years
- 37% had had joint surgery
  - » 15% synovectomy
  - » 13% arthrodesis
  - » 23% joint replacement
- 81% rheumatoid factor positive

Baseline Disease Characteristics

- 43% extra-articular manifestations
  - » 35% rheumatoid nodules
  - » 6% Sjogren's syndrome
  - » low prevalence vasculitis (<1%) and interstitial lung disease (2%)

Treatment Groups - ATTRACT

	Placebo	3mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts (428)	88	86	86	87	81

Discontinuations - Week 54

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Patients randomized	88	86	86	87	81
Patients discont'd	44 (50%)	23 (27%)	20 (23%)	12 (14%)	16 (20%)
Reason for discontinuation					
Adverse event	7 (8%)	5 (5.8%)	9 (10.5%)	4 (4.6%)	8 (9.9%)
Lack of efficacy	32 (36.4%)	17 (19.8%)	10 (11.6%)	6 (6.9%)	7 (8.6%)
Other	5	1	1	2	1

(Other includes patients who withdrew consent or discontinued due to noncompliance)

Review of Radiographic Data

Infliximab as a Treatment for Rheumatoid Arthritis - Prevention of Structural Damage

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Radiographic Protocol Schema

X-rays - Hands/Wrists & Feet

Timepoints

- Baseline
- 30 Weeks
- 54 Weeks

Primary Efficacy Endpoint at 54 Weeks

The Variable Analyzed

The Change from baseline to week 54 in the van der Heijde modification of the Total Sharp Score (TSS) according to two independent readers.

X-ray Interpretation Dataset

Two Blinded, Independent Reviewers

Two Separate Datasets

No Consensus Interpretations

Primary Efficacy Endpoint at 54 Weeks

For situations in which X-rays were interpreted by only one of the readers, the score of that reader was utilized for the statistical analysis.

Analysis of the Primary Endpoint

- Comparison of all treatment groups to placebo (at the 0.025 level)
- Improvement over the placebo (MTX-alone) group for at least 1 infliximab treated group (at the 0.025 level)

Population
Primary Efficacy Endpoint

Enrolled Study Population (428)

Patients with Paired, Evaluable X-rays (349)

- Hands & Feet
- Baseline & 54 Weeks
- Sufficient Image Quality for Reader Evaluation

Non-Evaluable Patients

	Placebo	3 mg/kg q8	3 mg/kg q4	10 mg/kg q8	10 mg/kg q4	Total
Pts randomized	88	86	86	87	81	428
Pts evaluated	64	71	71	77	66	349
Non-Evaluable Patients						
N	24	15	15	10	15	79
Complete set films but no TSS score obtained	3	2	4	2	2	13
Incomplete set x-rays	21	13	11	8	13	66

Analysis of the Primary Efficacy Endpoint

TSS: Hands & Feet

Erosion Score: Hands & Feet

Joint Space Narrowing: Hands & Feet

Total Sharp Score - Hands and Feet

Readers 1 & 2 — Change from Baseline: 0 - 54 Weeks

	Placebo	Infliximab Regimens + MTX				All
	MTX	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks	Infliximab Regimens
Patients Randomized	88	86	86	87	81	340
Patients Evaluated	64	71	71	77	66	285
Mean	6.95	1.29	1.63	0.16	0.71	0.61
(SD)	(10.30)	(6.02)	(8.48)	(3.61)	(3.83)	(5.86)
Median	4.00	0.50	0.09	0.50	-0.50	0.00
IQ range	(0.5, 9.7)	(-1.5, 3.0)	(-2.5, 3.0)	(-1.5, 2.0)	(-3.0, 1.5)	(-1.8, 2.0)
Range	(-4.5, 61.0)	(-9.8, 37.0)	(-23.0, 32.4)	(-11.5, 12.0)	(-13.4, 8.5)	(-23.5, 37.0)
p-value vs placebo		<.001	<.001	<.001	<.001	<0.001

Erosion Scores - Hands and Feet

Readers 1 & 2 — Change from Baseline - 54 Weeks

	Placebo	Infliximab Regimens + MTX				All
	MTX	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks	Infliximab Regimens
Patients Randomized	88	86	86	87	81	340
Patients Evaluated	66	72	74	79	68	293
Mean	4.03	0.17	0.29	0.17	-0.67	0.00
(SD)	(7.85)	(2.89)	(4.72)	(2.88)	(2.98)	(3.46)
Median	2.00	0.00	0.00	0.50	-0.50	0.00
IQ range	(0.5, 5.0)	(-1.4, 1.5)	(-1.5, 1.5)	(-1.5, 1.5)	(-1.8, 0.8)	(-1.5, 1.5)
Range	(-4.5, 53.2)	(-9.3, 9.0)	(-17.3, 19.8)	(-9.5, 13.8)	(-15.1, 7.2)	(-17.3, 19.8)
p-value vs placebo		<0.001	<0.001	<0.001	<0.001	<0.001

Joint Space Narrowing - Hands and Feet

Readers 1 & 2 — Change from Baseline - 54 Weeks

	Placebo	Infliximab Regimens + MTX				All
	MTX	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks	Infliximab Regimens
Patients Randomized	88	86	86	87	81	340
Patients Evaluated	64	71	71	77	66	285
Mean	2.86	1.06	0.65	-0.01	0.01	0.43
(SD)	(4.19)	(4.43)	(4.27)	(3.05)	(2.49)	(3.67)
Median	1.50	0.00	0.00	0.00	0.00	0.00
IQ range	(0.0, 5.8)	(-1.0, 2.0)	(-1.0, 2.0)	(-0.9, 1.0)	(-1.5, 1.0)	(-1.5, 1.0)
Range	(-4.5, 16.5)	(-7.0, 28.0)	(-16.0, 17.0)	(-15.6, 10.0)	(-5.5, 9.5)	(-16.0, 28.0)
p-value vs placebo		0.01	<0.001	<0.001	<0.001	<0.001

Sensitivity Analyses for Missing Patients

- Worst Case Analysis
- Worst Outcome Analysis
- Worst Outcome Analysis (modified)
- % Radiographic Progression

Worst Case Analysis (Placebo -23.50, Infliximab 61.03)

Total Sharp Score - Hands and Feet
Change from Baseline: 0 - 54 Weeks

	Placebo	Infliximab		Regimens	+ MTX
	MTX	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks
Patients Evaluated	64	71	71	77	66
Patients Randomized	88	86	86	87	81
Mean (SD)	-1.35 (16.21)	11.71 (23.45)	11.99 (23.94)	7.15 (19.82)	10.72 (24.38)
Median	1.25	1.00	1.00	0.56	0.00
IQ range	(-23.5, 7.4)	(-1.0, 6.5)	(-1.5, 11.0)	(-1.5, 2.5)	(-1.7, 4.0)
Range	(-23.5, 61.0)	(-9.8, 61.0)	(-23.5, 61.0)	(-11.5, 61.0)	(-13.4, 61.0)
p-value vs placebo		0.135	0.106	0.795	0.594

Worst Outcome Analysis

All Missing Subjects received 61.03

Total Sharp Score - Hands and Feet
Change from Baseline: 0 - 54 Weeks

	Placebo	Infliximab		Regimens	+ MTX
	MTX	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks
Patients Evaluated	64	71	71	77	66
Patients Randomized	88	86	86	87	81
Mean (SD)	21.70 (25.76)	11.71 (23.45)	11.99 (23.94)	7.15 (19.82)	10.72 (24.38)
Median	8.63	1.00	1.00	0.56	0.00
IQ range	(2.0, 61.0)	(-1.0, 6.5)	(-1.5, 11.0)	(-1.5, 2.5)	(-1.7, 4.0)
Range	(-4.5, 61.0)	(-9.8, 61.0)	(-23.5, 61.0)	(-11.5, 61.0)	(-13.4, 61.0)
p-value vs placebo		<0.001	<0.001	<0.001	<0.001

Worst Outcome Analysis (Modified)

Missing Infliximab Patients Given Worst Outcome (61.03)
Missing Placebo Pts Given Placebo Median (4.00)

Total Sharp Score Hands and Feet - Change from Baseline - 54 Weeks

	Placebo	Infliximab Regimens + MTX			
	MTX	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks
Patients Evaluated	64	71	71	77	66
Patients Randomized	88	86	86	87	81
Mean (SD)	6.15 (8.86)	11.71 (23.45)	11.99 (23.94)	7.15 (19.82)	10.72 (24.38)
Median	4.00	1.00	1.00	0.56	0.00
IQ range	(-2.0, 7.4)	(-1.0, 6.5)	(-1.5, 11.0)	(-1.5, 2.5)	(-1.7, 4.0)
Range	(-4.5,	(-9.8,	(-23.5,	(-11.5,	(-13.4,
p-value vs placebo		0.004	0.014	<0.001	<0.001

Percent Radiographic Progression

Change in Total Sharp Score > 0 = Progression
If Total Sharp Score is Missing = No Progression

Total Sharp Score - Hands and Feet
Change from Baseline: 0 - 54 Weeks

	Placebo	Infliximab Regimens + MTX			
	MTX	3 mg/kg q 8 Wks	3 mg/kg q 4 Wks	10 mg/kg q 8 Wks	10 mg/kg q 4 Wks
Patients Evaluated	64	71	71	77	66
Patients Randomized	88	86	86	87	81
Progression (%)	51 (58%)	37 (43%)	36 (42%)	40 (46%)	22 (27%)
p-value vs placebo		0.0470	0.0340	0.1130	0.0010

Summary of Other Analyses

Hands Only
TSS Erosions JSN

Feet Only
TSS Erosions

Feet Only
JSN

Summary of Other Analyses

Prevention of Radiologic Progression

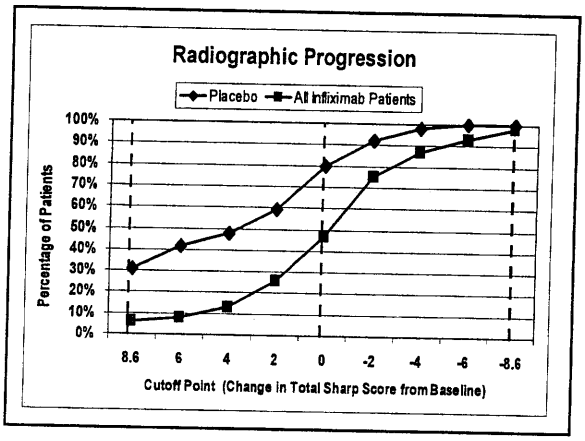
Prevention of Radiologic Progression

Prospectively defined in the protocol as an increase from baseline in the van der Heijde modification of the Sharp score greater than the inter-observer measurement error of progression (SDD) between the two readers as...

Prevention of Radiologic Progression

determined by using the limits of agreement methods of Bland and Altman, 1985 (SDD).

The SDD was calculated from the two blind interpretation datasets for this trial as approximately 8.6.


Radiographic Progression
Placebo
All Infliximab Patients
Percentage of Patients
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
8.6
6
4
2
0
-2
-4
-6
-8.6
Cutoff Point (Change in Total Sharp Score from Baseline)

Review of Clinical Data

Review of Clinical Data

- Efficacy Data - week 54
  - » ACR Response
  - » Improvement in Disability
  - » Clinical & Radiographic Response
- Safety Data
  - » Week 54

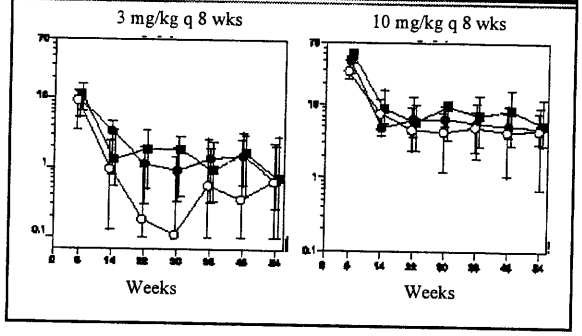
ACR20 Response at Weeks 30 and 54

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts	88	86	86	87	81
ACR20 Responders					
Wk 30	18 (21%)	43 (50%)	43 (50%)	45 (52%)	47 (58%)
Wk 54	15 (17%)	36 (42%)	41 (48%)	51 (59%)	48 (59%)

Durability of ACR20 Response

	Plac	3 q 8 wks	3 q 4 wks	10 q 8 wks	10 q 4 wks
Total Pts	88	86	86	87	81
Wk54 and wk30	12 (14%)	28 (33%)	34 (40%)	37 (43%)	38 (47%)
Wk54 but not wk30	3 (3%)	8 (9%)	7 (8%)	14 (16%)	10 (12%)
Wk30 but not wk54	6 (7%)	15 (17%)	9 (11%)	7 (8%)	9 (11%)

Infliximab Concentrations - ACR Response



HAQ

- 8 categories: dressing & grooming, arising, eating, walking, hygiene, reach, grip, and activities
- Score 0-3 for series of 2-4 questions per category
- 0 = normal, 1 = adequate, 2 = limited, 3 = unable to perform task
- Final score range 0-3

AUC Measurement of Functional Outcome

Weighted mean HAQ through wk54 - sum of mean HAQ score for each observation period, divided by the total time of observation

Landmark Analysis - HAQ

All Patients – last obvservation carried forward

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts	87	86	85	87	81
Mean ± SD	0.2 ± 0.6	0.4 ± 0.6	0.5 ± 0.6	0.6 ± 0.6	0.4 ± 0.6
Median	0.1	0.4	0.5	0.5	0.3

Clinical & Radiographic Progression

- Definition of radiographic progression
- Clinical Response
  - » ACR20
  - » AUC-HAQ

ACR Response & Change from Baseline X-ray Score

All infliximab treated patients at week 54

	ACR20 Response		Total
X-ray progression*	Yes	No	
No	91	59	150
Yes	85	105	190
Total	176	164	340

*X-ray progression defined as an increase from baseline van der Heijde score or a missing score.

Correlation between ACR and Change in X-ray Score

	All Infliximab		Placebo	
ACR response	N	mean change in x-ray score	N	mean change in x-ray score
ACR20				
No	122	1.25	50	7.20
Yes	163	0.12	14	6.04
ACR50				
No	180	1.14	57	7.06
Yes	105	-0.31	7	6.06

HAQ and Change in X-ray Score

	All Infliximab		Placebo	
Range AUC-HAQ response	N	mean change in x-ray score	N	mean change in x-ray score
≤ 90%	249	0.67	60	7.45
>90%	35	0.09	3	-2.00

Review of Safety Database

- Week 54 ATTRACT
  - » deaths
  - » malignancies
  - » infections
  - » autoimmune
  - » infusion reactions

Deaths through Week 54 - ATTRACT

- 8 Deaths
  - » 5 through wk 30, 3 after wk 30
  - » 3 patients received placebo
  - » 5 patients received infliximab -
    - · 1 patient/dosing regimen;
    - · 2 in 3 mg/kg q4

Cause of Deaths - week 54

- Placebo: intestinal gangrene, arrhythmia, cardiac failure
- Infliximab:
  - » pulmonary embolism
  - » cardiopulmonary (2 pts)
  - » tuberculosis
  - » coccidioidomycosis

Malignancies - Week 54 ATTRACT

- 5 patients diagnosed with malignancy
  - » 3 cases reported by week 30
  - » all received 10 mg/kg Infliximab

Malignancies - Week 54

- 3 patients treated with 10 mg/kg q 4 weeks
  - » large cell lymphoma
  - » recurrent breast carcinoma
  - » squamous cell & melanoma (same patient)

Malignancies - Week 54

- 2 patients treated with 10 mg/kg q 8 weeks
  - » basal cell carcinoma
  - » rectal adenocarcinoma

Infections

	Placebo	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts treated	86	88	86	87	81
Pts with any infection	52 (61%)	60 (68%)	58 (67%)	66 (80%)	64 (79%)
Pts with infections treated w/ antibiotics	30 (35%)	30 (34%)	35 (41%)	46 (53%)	38 (47%)
Pts with ≥1 serious infections	7 (8%)	2 (2%)	6 (7%)	7 (8%)	6 (6%)

Serious Infections in ≥ 2 Infliximab-treated Patients

	Placebo	All Infliximab
Pts treated	86	342
Pneumonia	1	5
Cellulitis	0	3
Pyelonephritis	0	2
Infection - bacterial	0	2
Sepsis	2	2
Herpes zoster	0	2

Autoimmune Disease

- One case of drug-induced lupus through Week 54
  - » 48 YO female, RA for 18 years
  - » 10 mg/kg q 8 weeks infliximab
  - » rash - 2 wks after wk2 infusion
    - · by month 3 resolved; recurred 1 month later
  - » weakly positive ANA; negative anti-dsDNA

Infusion Reactions - Week 54

	Plac	3 mg/kg q 8 wks	3 mg/kg q 4 wks	10 mg/kg q 8 wks	10 mg/kg q 4 wks
Pts treated	86	88	86	87	81
Infusions w/ infusion Rx	17 (2%)	22 (3%)	55 (5%)	36 (5%)	26 (2%)
Pts with ≥ 1 infusion Rx	10 (12%)	16 (18%)	22 (26%)	19 (22%)	17 (21%)

Postmarketing Reports - Infections

- 130 total, 21 deaths
  - » 10 pneumonia
  - » 29 upper respiratory (bronchitis, sore throat, cough, sinusitus)
  - » 19 sepsis
  - » 5 tuberculosis
  - » 10 fungal (aspergillus, histoplasma, PCP, candida)
  - » 9 viral (H. simplex, CMV)

Summary

- Efficacy
  - » Delay in progression of structural damage through week 54
    - · both erosion and joint space narrowing
  - » Durable clinical response (ACR20) through week 54

Summary

- Safety
  - » Infection rate higher in infliximab-treated patients
    - serious infections comparable to placebo
  - » Risk of infusion reactions
  - » No increase incidence of safety events between weeks 30 & 54